REMARKS

Claims 1-7 and 9 are pending in this application. Claims 7 and 9 are withdrawn. Claims 1, 2 and 4-6 stand rejected. Claims 3-5 are objected to. Claims 4-5 are canceled herein without prejudice. Claim 3 is amended herein to delete the structure objected to by the Examiner. No new matter is added by way of this amendment. Entry of the claim amendments and reconsideration in view of the following remarks are respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 1, 2 and 4-6 stand rejected under 35 U.S.C. § 103(a) over Goulet et al. (U.S. 6,329,380) for reasons of record. Applicants traverse the rejections for reasons of record as well as at least the following reasons.

The Examiner rejects as unpersuasive the Applicants' arguments that the substituent Z is *functionally* different from the homologous substituent in Example 48 described by Goulet et al., in that it can function as a Michael acceptor and react with the crucial cysteine residue in the JAK kinase to be inhibited. The Examiner took the position that, in the absence of convincing side-by-side data demonstrating unobviousness, the claims are considered *prima facie* obvious.

Accompanying this response is the Declaration of Christopher John Burns under 37 C.F.R § 1.132 (hereinafter "Burns Declaration"), along with supporting Exhibits A-C. Dr. Burns is a co-inventor of the instant application.

As indicated in the enclosed declaration, benzimidazole compounds substituted with a group, Z, which can function as a Michael acceptor, were designed to interact irreversibly with a cysteine residue in the putative ATP binding site of JAK3. See Burns Declaration, ¶ 4. The predicted binding mode was analyzed by *in silico* screening and then verified by *in vitro* binding experiments. See Burns Declaration, ¶ 3.

As understood by those of ordinary skill in the art, to function as Michael an acceptor, a compound generally needs to possess α,β-unsaturation such that a Michael donor can undergo nucleophilic addition to the β-carbon atom. See Burns Declaration, ¶ 5. Examples of suitable Michael acceptors, as well as groups lacking the requisite unsaturation that are otherwise structurally comparable, are shown in Exhibit B. See Burns Declaration, ¶ 5 and Exhibit B

Exhibit C includes JAK2 and JAK3 IC_{50} data for compounds possessing α,β-unsaturation and comparator compounds that lack the conjugated olefin functionally. See Burns Declaration, ¶¶ 6-7 and Exhibit C. The comparative examples provided in Exhibit C clearly show that compounds containing α,β-unsaturation, which are capable of acting as Michael acceptors, are significantly more potent inhibitors of JAK3 than otherwise similar compounds that lack the α,β-unsaturation. See Exhibit C.

For example, compound **1**, which is a known Michael acceptor, is greater than 10-fold more potent as a JAK3 inhibitor than compound **2**, which cannot function as a Michael acceptor. See Burns Declaration, ¶ 8. Similarly, a comparison of compounds **3, 4** and **5** demonstrates that compounds **3** and **4** are greater than 10-fold more potent inhibitors of JAK3 relative to compound **5**. *Id.* Compounds **3** and **4** contain α,β-unsaturated double and triple bonds, respectively, and can therefore function as Michael acceptors, while compound **5** is saturated and cannot function as Michael acceptor. *Id.* These data provide clear evidence supporting the hypothesis that incorporating a moiety that can function as a Michael acceptor at a position designed to interact with the cysteine residue of the putative ATP binding site greatly increases the JAK3 inhibitory potency. See Burns Declaration, ¶ 9.

One of skill in the art would understand that Example 48 of Goulet et al. is not capable of functioning as a Michael acceptor because the olefinic bond is not conjugated to the carbonyl moiety (i.e., Example 48 contains β,γ-unsaturation, not the required α,β-unsaturation). The enclosed declaration and exhibits clearly exemplify the types of moieties that function as Michael acceptors, and demonstrate that replacing the α,β-unsaturated

functionality with a group which is "visually" similar to the Michael acceptor results in a significant decrease in JAK3 inhibitory potency. In view of the binding data provided in Exhibit C, one of skill in the art would not reasonably expect Example 48 of Goulet et al. to be a potent inhibitor of JAK3, as the compound lacks the α,β-unsaturation and would not be capable of performing the intended use of the compounds as presently claimed.

The Examiner rejects as unpersuasive the argument that the present compounds were designed as JAK inhibitors, whereas Goulet et al.'s compounds were designed as SRC inhibitors, stating that the recitation of intended use must result in a structural difference in order to patentably distinguish the claimed compounds from Goulet et al. The Examiner cites *Takeda Chem. Indus.* for the proposition that it is widely accepted that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed composition or compounds, creates a *prima facie* case of obviousness..." *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007).

Applicants respectfully submit that the required presence of a α,β-unsaturated moiety in the claimed compounds is a structural difference that distinguishes the claimed compounds from Example 48 of Goulet et al. Moreover, as the Federal Circuit recently reaffirmed in *Eisai v. Dr. Reddy's Laboratories Ltd.*, 87 USPQ.2d 1452 (Fed. Cir. 2008), in chemical compound cases, "[o]bviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound. *Id.* at 1455 (citing *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007)).

Thus, in order to establish a *prima facie* case of obviousness for a chemical compound, the Office must first provide a reasoned identification of a "lead compound", and then provide a motivation that would lead one of ordinary skill in the art to modify the lead compound in a particular way to achieve the claimed compounds. Applicants respectfully

submit that the Office has done neither, and accordingly has failed to establish a *prima facie* case of obviousness in the instant case.

First, no reason has been provided to suggest why one of ordinary skill in the art would have selected Example 48 of Goulet et al. as the starting point in the search for novel JAK kinase inhibitors. As previously noted by the Applicants, the SRC portion of the human tyrosine kinase family is on a different branch of the TK limb as compared to JAK, and SRC is just one of 518 human kinases. Thus, one of skill in the art could not have reasonably expected that a SRC inhibitor would inhibit a JAK kinase, or vice versa. In addition, Goulet et al. provide no biological data for the compound of Example 48, stating only that certain compounds have IC_{50}'s less than 10 μM in one of the described assays, which do not include assays related to JAK kinases. See Goulet et al., col. 28, lines 51-58.

Of the 70 examples disclosed by Goulet et al., no guidance has been provided that would lead one of skill in the art to specifically select Example 48 as a 'lead compound' for optimization of activity against another, distantly related kinase. Goulet et al. taken as a whole provides no suggestion of the necessity for including a Michael acceptor as a substituent on the benzimidazole. None of the possible embodiments provided would serve this function and none of the exemplified compounds set forth in Goulet et al., including Example 48, have this ability. Thus, Goulet et al. provide no guidance that would have led one of ordinary skill in the art to make the specific structural modifications to Example 48 required to arrive at the present invention, out of the myriad number of possible modifications that could have been made to this structure. Accordingly, in this particular instance, it is clear that mere homology is insufficient to suggest the compounds of the present invention.

Moreover, the compounds of the present invention, which contain a α,β-unsaturated functionality attached to the benzimidazole ring, demonstrated a greater than 10-fold increase in JAK3 inhibitory activity relative to comparable compounds lacking this critical feature. Applicants respectfully submit that the significant increase in JAK3 potency provided by the compounds of the present invention, as claimed, could not have been expected based on Goulet et al.

In view of the foregoing remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Rejection for Obviousness-type Double Patenting

Claims 1, 2 and 4-6 remain rejected for obviousness-type double patenting over co-pending application 10/581,412. The rejection was maintained because the terminal disclaimer submitted with the response filed October 9, 2009 had not yet been approved when the instant Office action was issued. Applicants traverse the rejection.

Applicants respectfully note that the terminal disclaimer file October 9, 2009 has been approved by the Office, effective November 6, 2009. Accordingly, Applicants believe this basis of rejection is overcome and may be properly withdrawn.

Objection to the Specification – Abstract

The Abstract of the disclosure is objected to as failing to exemplify any members or illustrative formulae of the claimed class.

The Abstract is amended herein to include the structure of Formula I, as suggested by the Examiner. Applicants respectfully request that the objection to the specification be withdrawn.

Claim Objections

Claim 3 is objected to because the species shown on page 7 of the Office Action is not a substituted benzimidazole of Formula I and there does not comply with the Requirement for Restriction/Election of Species mailed April 13, 2009. Claim 4 is objected to because the recitation of intended use of a substituted benzimidazole of formula I as an irreversible inhibitor of JAK3 allegedly fails to result in a structural difference and is not given patentable weight. Claim 5 is objected to because the recitation of an intended use of a benzimidazole of formula I as a selective inhibitor of JAK3 allegedly fails to result in a structural difference and is not given patentable weight. Applicants traverse the objections.

Solely to advance prosecution, claims 4 and 5 are canceled herein. Claim 3 is amended herein to delete the structure objected to by the Examiner. Accordingly, Applicants respectfully request that the claim objections be withdrawn.

As the claims to the compositions are believed to be in a position for allowance, rejoinder and allowance of claims 7 and 9 is also respectfully requested.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 415850001100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: January 27, 2010 By: / Leslie A. Robinson /

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